A COMPARATIVE STUDY OF EFFECT OF ADDITION OF 25µg SUFENTANIL OR 100mg TRAMADOL TO 0.5% LIGNOCAINE IN INTRAVENOUS REGIONAL ANAESTHESIA FOR HAND SURGERIES

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CERTIFICATE

This is to certify that dissertation entitled "A comparative study of effect of addition of 25μg sufentanil or 100mg tramadol to 0.5% lignocaine in intravenous regional anaesthesia for hand surgeries" is the bonafide record of work done by Dr.M.BALAMURUGAN in the Department of Anaesthesiology, Thanjavur medical college, Thanjavur, during his post graduate course from 2004-2007.This is submitted as partial fulfillment for the requirement of M.D. degree Examination - Branch X(Anaesthesiology) to be held in march 2007.

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INTRODUCTION

Intravenous regional anaesthesia is a regional technique in which analgesia and muscle relaxation are produced by the injection of an adequate volume of local anaesthetic solution into a vein of an extremity with inflow and outflow of the blood prevented by proximally applied tourniquet.

The history of intravenous regional anaesthesia had begun with August Bier, who described the technique in 1908. But in 1970 after a lapse of 62 years, the technique was modified and popularized by Holmes as “Bier Block”

Lignocaine has been the drug most frequently used for intravenous regional anaesthesia, as it is the only drug approved for intravenous regional anaesthesia. Lignocaine is considered as a less toxic local anesthetic. It is used intravenously for treating ventricular arrhythmias in the dose of 1-2mg/kg safely and also used for attenuating stress response to endotracheal intubation.

However in intravenous regional anaesthesia toxic reactions like convulsions, coma, cardio respiratory depression and cardiac arrest has been reported following its use. Toxicity may be due to leakage of the drug past the tourniquet after the injection because of either tourniquet failure or buildup of excessively high venous pressure distal to the tourniquet.

Intravenous regional anaesthesia has been limited by tourniquet pain and inability to provide postoperative analgesia. To improve quality of

intravenous regional anaesthesia various drugs like ketorolac, morphine, meperidine, tramadol, fentanyl, sufentanil and small dose of muscle relaxants like pancuronium and atracurium have been added to lignocaine.

In our study it was decided to evaluate the efficacy of sufentanil 25µg or tramadol 100mg added to 0.5% lignocaine in reducing sensory block onset and recovery time, motor block onset and recovery time, duration of post operative analgesia, tolerance to tourniquet pain and requirement of postoperative analgesic drugs.

AIM OF THE STUDY

The aim of the study is to evaluate the efficacy of 25µg sufentanil added to 0.5% lignocaine and 100mg tramadol added to 0.5% lignocaine in intravenous regional anaesthesia for hand surgeries.

ANATOMY OF SUPERFICIAL VEINS OF UPPER LIMB

The venous supply of the upper limb is arranged in two planes, which are separated by superficial aponeurosis. The superficial venous system is used for intravenous regional anesthesia.

The dorsal digital veins converge to form three dorsal metacarpal veins that are interlinked to each other. The palmar digital veins drain into dense vascular network on the palmar face of the hand and also into dorsal digital veins by way of intercapillary veins. Most of the superficial veins join to form two large veins, the cephalic vein and the basilic vein, which present several anatomic variations. An accessory cephalic vein is often present.

The cephalic vein is the preaxial vein of the upper limb. It begins from the lateral end of the dorsal venous arch. The cephalic vein runs upward through the root of the anatomic snuff box, and winds around the lateral border of the dorsal forearm. In the proximal part of the forearm, the cephalic vein runs medially to run along the anterior aspect of the forearm. Here, several branches from palmar plexus of veins join it.

At the level of elbow, it runs between the tendons of brachioradialis

and the biceps brachii, crosses the lateral cutaneous nerve of forearm and then runs along the lateral border of the biceps. It then pierces the deep fascia at the lower border of pectoralis major and then runs in the deltopectoral groove up to the infraclavicular fossa where it pierces the clavipectoral fascia and joins the axillary vein.

The accessory cephalic vein, when present rises from a venous network on the back of the forearm or from the lower part of cephalic vein. It joins the cephalic vein below the elbow or in front of the elbow. when main cephalic vein drains into the basilic vein, the accessory cephalic vein may follow the course of the former above the elbow.

The basilic vein is the postaxial vein of the upper limb and arises from the medial end of the dorsal venous arch a little below thumb. It runs upward along the back of the medial border of the forearm, winds around this border to reach the ventral aspect of cubital fossa and then runs along the medial aspect of the biceps brachii up to the middle of the arm, pierces the deep fascia and runs along the medial side of the brachial artery, up to the lower border of the teresmajor where it continues as axillary vein. About 2.5 cm above the medial condyle of the humerus, the basilic rein joined by the medial cubital vein. It is accompanied by the posterior branch of the medial cutaneous nerve of the forearm and the terminal part of the dorsal branch of

the ulnar nerve.

The superficial palmar venous network is drained by median vein of forearm, which runs along the anterior aspect of the forearm, in front of the elbow, it drains directly into basilic vein.

ANATOMY OF NERVE

Neurons in human central nervous system are in many different size and shapes. These cells have five to seven processes called dendrites that extend outward from the cell body and arborize extensively. A typical neuron also has a long fibrous axon that originates from a thickened area of cell body called as axon hillock. The first portion of the axon is called as initial segment. The axon divides into terminal branches ending in a number of synaptic knobs.

The axons are wrapped by a sheath of myelin, a protein rich complex produced by schwann cells. The myelin sheath envelops the axon except at its ending or the nodes of Ranvier, a periodic 1-μm constriction that are about 1mm apart.

There are some neurons are unmyelinated, which are simply surrounded by schwann cells without the wrapping of schwann cell membrane around the axon.

PHYSIOLOGY OF NERVE CONDUCTION

ACTION POTENTIAL

The resting membrane potential of the nerve is about – 70 mV. If the axon is stimulated and a conducted impulse occurs, a series of potential changes occurs, which is known as action potential.

The first manifestation of approaching action potential is a beginning of depolarization of membrane. After initial 15mV of depolarization, the rate of depolarization increases, the point called as threshold. Thereafter rapidly reaches and overshoots to +35mV.It then reverses and falls rapidly towards resting level. The sharp rise and fall are spike potential of axon, and slower fall at the end of process is after depolarization. After reaching the previous resting level, there is prolonged hyper polarization called after-hyper polarization. During the phase of spike potential, the neuron is refractory to stimulation called as absolute refractory period.

IONIC FLUXES DURING ACTION POTENTIAL

During action potential, there is opening of Na^+ channels and Na^+

enters into the nerve cell. The Na^+ channels rapidly enter into a closed state called as inactivated state and then returning to resting state.

During repolarization there is opening of voltage gated K^+ channels, and K^+ moves out of cell. The net movement of positive charge out of the cell due to K^+ efflux helps to complete the process of repolarization. The slow return of K^+ channels to closed state is responsible for after – repolarization.

OPIOID RECEPTORS

The opioid receptors are classified as mu (μ), delta (δ) and kappa (κ) receptors. These receptors are belonging to super family of guanine (G) protein coupled receptors.

μ receptors or morphine preferring receptors are principally responsible for supraspinal and spinal analgesia. Activation of subpopulation μ receptors (μ_1) is responsible for analgesia, where as μ_2 receptors are responsible for hypoventilation, bradycardia and physical dependence. The beta endorphins are endogenous ligand for μ receptors. The exogenous ligands for these receptors are morphine, fentanyl, alfentanil, sufentanil and remifentanil.

Endogenous agonists for kappa receptors are dynorphins. Activation of these receptors resulting in inhibition of neurotransmitter release via type N calcium channels. Respiratory depression is less with kappa receptor

although dysphoria and diuresis may occur.

Delta receptors respond to the endogenous ligands, encephalins and these receptors may serve to modulate the activity of μ receptors.

PERIPHERAL OPIOID RECEPTORS

Pain can be effectively diminished by various endogenous mechanisms within the central nervous system. One region where these mechanisms have been well characterized is the dorsal horn of the spinal cord, in which impulses from peripheral nerves are modulated before they are transmitted centrally to evoke perception and response. Recent research has shown that, in addition to these mechanisms in the central nervous system, intrinsic modulation of nociception can occur at the peripheral terminals of afferent nerves. Specifically, the immune system can interact with peripheral sensory-nerve endings to inhibit pain

Notwithstanding the traditional view that opioid antinociception takes place exclusively within the central nervous system, there are peripheral opioid receptors that mediate analgesic effects when activated by exogenous opioid agonists applied locally. Such effects are particularly prominent in painful inflammatory conditions. The opioid receptors on peripheral sensory

nerves are up regulated during inflammation. Their endogenous ligands - opioid peptides - are expressed by the resident immune cells in inflamed peripheral tissue. Environmental stimuli and endogenous substances, such as corticotropin-releasing hormone and cytokines, can stimulate the release of these opioid peptides, resulting in local analgesia. Suppression of the immune system abolishes these effects. Thus, it is likely that endogenous opioid peptides can be secreted from immune cells, occupy opioid receptors on sensory nerves, and cause analgesia by inhibiting either the excitability of these nerves or the release of excitatory, proinflammatory neuropeptides.

Opioids bind to receptors on dorsal-root ganglia, the central terminals of primary afferent neurons, and peripheral sensory-nerve fibers and their terminals. The characteristics of these receptors are very similar to those in the brain. Dorsal-root ganglia contain messenger RNA (mRNA) for opioid receptors, and primary afferent nerves mediate the peripheral antinociceptive effects of opioid.

Opioid agonists have easier access to neuronal opioid receptors during inflammation because inflammation disrupts the perineurium (normally a rather impermeable sheath encasing peripheral-nerve fibers) and because the number of peripheral sensory-nerve terminals is increased in inflamed tissue,

a phenomenon known as sprouting. In addition, previously inactive neuronal opioid receptors may become active in the inflammatory milieu.

Peripherally acting opioids would allow analgesia without central side effects, such as dysphoria, respiratory depression, sedation, nausea, or addiction, and without the side effects either of nonsteroidal anti inflammatory drugs (e.g., renal toxicity and gastric bleeding) or of local anesthetic drugs (motor- and autonomic-nerve blockade). Whether tolerance to the analgesic effects of peripherally active opioids develops is not known. The fact that peripheral opioid actions are particularly prominent in inflamed tissue may be clinically advantageous, considering that many painful conditions, sub acute or chronic, are associated with inflammation (for example, trauma, postoperative pain, pain due to cancer, and arthritis).

PHARMACOLOGY

LIGNOCAINE

Lignocaine is one of an amide group local anesthesia. It is diethyl aminiacetyl 2, 6-xylidine hydrochloride monohydrate.

PHYSICAL PROPERTIES

Lignocaine is a weak base with pK value of 7.9.At the pH of 7.4 lignocaine has 25 % of non ionized fraction. It has the protein binding capacity of 70%.

MECHANISM OF ACTION

Lignocaine prevents transmission of nerve impulse by inhibiting passage of sodium ions through ion-selective sodium channels in nerve membrane. Lignocaine selectively binds to sodium channels in inactivated closed states and there by stabilizes these channels in this configuration and prevent their change to rested closed and activated - open states in response to nerve impulse.

METABOLISM

The principal metabolic pathway of lignocaine is oxidative dealkylasion in liver to monoethyl glycine xylidide followed by hydrolysis

to xylidide. Approximately 75% of xylidide is excreted in the urine as 4 hydroxy 2, 6- dimethylaniline.

SIDE EFFECTS

Apart from Na^+ channels, lignocaine binds many other targets including voltage-gated K^+ and $Ca2^+$ channels, K^+ ATP channels, enzymer, NMDA receptors and nicotinic acetylcholine receptors. Binding of lignocaine to these sites may contribute toxic side effects.

CENTRAL NERVOUS SYSTEM TOXICITY

Lignocaine at low concentrations likely to produce numbness of the tongue and circumoral tissues. As plasma concentration increases restlessness, vertigo, tinnitus and difficulty in focusing may occur initially. Further increase in the concentration result in slurred speech, skeletal muscle twitching, drowsiness and seizures that due to selective depression of inhibitory cortical neurons leaving excitatory pathways unopposed.

CARDIOVASCUTLAR TOXICITY

Cardiovascular system is more resistant to toxic effect of lignocaine than central nervous system. At plasma concentration 5-10μg/ml, lignocaine may produce profound hypotension and direct myocardial depression.

TRAMADOL

Tramadol hydrochloride is a new centrally acting synthetic opioid. It possesses opioid agonist properties and activates mono aminergic spinal mechanism of inhibition of pain. The analgesic property of tramadol is combined with low respiratory depressant effect and low dependence potential.

Tramadol hydrochloride is (+, -) trans-2-dimethyl aminomethyl-1-m-methoxyphenyl-cyclohexanol hydrochloride.

Molecular formula $C_{16}H_{25}O_2NHCl$

CHEMISTRY OF TRAMODAL

Tramadol is a synthetic 4-phenyl piperidine analogue of codeine. It has pure opioid agonistic property with no antagonistic property. Tramadol like codeine has a methyl substitution on the phenolic moiety of the morphine structure, which explains its relative weak affinity for opioid receptor. It has selective affinity for μ receptors. The O-desmethyl metabolite of tramadol has 2-4 times analgesics potency of the parent compound and 4 to 200 times greater affinity for μ receptors than the parent compound.

MECHANISM OF ACTION

Tramadol produces its anti nociceptive effect by two different but synergistic analgesic actions.

Opioid action: Tramadol is a μ opioid receptor agonist. However the affinity for μ opioid receptor is 6000 fold less than morphine and 10 fold

less than codeine. Tramadol acts only on μ_1 thus it does not cause respiratory depression as an adverse effect.

Non-opioid action: Tramadol inhibits the reuptake of serotonin and nor adrenaline in the descending spinal inhibitory pathway enhancing effectiveness of the inhibitory pathway. These neurotransmitters in the descending pathways enhance the analgesic response without inducing adverse effects on cardiovascular and respiratory system. Tramadol combines the mechanism of action of opioids and tricyclic antidepressants.

PHARMACOKINETICS

Tramadol is metabolized in the liver by two main metabolic pathways to form N and O desmethylated compounds (Phase I reaction). The O desmethylated metabolites are further conjugated (Phase II reactions). A total of 11 metabolites have been identified, 5 from phase I reaction and 6 from phase 11 reaction. Apart from O desmethyl tramadol M_1 all the other metabolites are pharmacologically inactive. Production of M_1 is dependent on the CYP_2D_6 isoenzyme of the cytochrome p450 enzyme system.

Tramadol and its metabolites are excreted primarily in the urine. The mean ± SD terminal elimination half lifes of tramadol and its metabolite M_1 are 6.3 ± 1.4 and 7.4 ± 1.4 hrs respectively in healthy young adults whether the drug is administered orally or intravenous. Hepatic impairment and renal

insufficiency results in prolongation of elimination half lives of tramadol. Serum concentration after 100 mg intravenous of tramadol at 15 min and 2 hrs are 613 and 409 μg/ml.

PHARMACODYNAMICS

Analgesic property

The analgesic activity of tramadol hydrochloride is attributable to both parent drug and its M_1 metabolite. Serum tramadol concentration of 100-300 μg/ml is required for analgesic activity. It is effective in treating acute pain like post operative pain, labour pain, ureteric colic, dental pain, acute myocardial infarction, angina, traumatic injuries and in chronic pain like cancer pain and osteoarthritis.

Respiratory System

Minimal changes in respiratory rate and tidal volume when compared to morphine and no respiratory depression.

Cardiovascular System

The healthy volunteers intravenous bolus doses of tramadol 100 mg causes an increase in heart rate of 7-10 beats/min and increase in systolic and diastolic blood pressure of 6 and 14 mm Hg respectively over a period

of 5-8 minutes after injection. These changes are returned to normal values by 15 minutes.

Gastrointestinal System

Tramadol may produce nausea, vomiting constipation and dry mouth. However these adverse effects are particularly likely to occur after rapid intravenous injection. To prevent these effects intravenous tramadol is best administered slowly.

Physical Dependence

Unlike morphine or pethidine tramadol has least addiction potential.

OTHER EFFECTS

Tramadol 1 mg/kg intravenously reduces post anesthetic and spinal shivering. It has dose dependent antitussive effects.Tramadol has a weak antioedema action.

DOSAGE AND ADMINISTRATION

Tramadol can be administered through oral, parenteral, epidural and intrathecal routes. The dose is 1-2 mg/kg whether administered intramuscular, intravenous, oral or epidural. Maximum recommended dose is 400 mg/day.

ADVERSE EFFECTS

Tramadol causes non-specific irritation, sedation (very mild when

compared to other opioids), headache and seizure.

Tramadol may produce nausea, vomiting, constipation and change in appetite. It will cause tachycardia, dry mouth, sweating, and allergic skin reaction.

SUFENTANIL

Sufentanil is a phenylpiperidine series of synthetic opioid which is thienyl analogue of fentanyl.

PHYSICAL PROPERTIES

The pKa of sufentanil is 8.0. The percentage of nonionised fraction at pH 7.4 is 20%. The protein binding capacity of sufentanil is 93%. It primarily binds to alpha 1 acid glycoprotein. The partition coefficient of sufentanil is 1,727.

Volume of distribution of sufentanil is 123litres.Clearance of sufentanil is 900ml/min. the elimination half-life is 2.2- 4.6 hours. Context sensitive half-life is 30 minutes

DOSE

Sufentanil given in the dose of 0.1-0.4 μg /kg for intravenous route. For intrathecal administration sufentanil given in the dose 0.01-0.06 μg single dose.

METABOLISM

Sufentanil has high hepatic extraction ratio. It undergoes significant first pass pulmonary uptake after rapid intravenous injection.

Sufentanil rapidly metabolized by N-dealkylasion at piperidine nitrogen and by o-demethylation. Less than 1% of an administered dose of sufentanil appeared unchanged in the urine.

PHARMACOGICAL PROPERTIES

ANALGESIC PROPERTY

The analgesic effects of sufentanil are similar to morphine. Sufentanil is approximately 1000 times more potent than morphine. Sufentanil is far more lipid soluble than morphine, thus the risk of delayed respiratory depression from rostral spread of intrathecal opioid is greatly reduced.

The peak analgesic effect of sufentanil after intravenous administration is 5min. Recovery from analgesic effects also occurs more quickly.

OTHER CNS EFFECTS

As with other μ opioids nausea, vomiting and itching can be observed with sufentanil.

Muscle rigidity is more common after administration of sufentanil. This effect is felt to be centrally mediated. Rigidity can be mitigated by avoiding bolus dosing, slower administration of boluses and pretreatment

with a non-opioid anesthetic induction agent. Respiratory depression is similar to other opioid but onset is more rapid and short duration.

CARDIOVASCULAR EFFECTS

Sufentanil decreases heart rate and mildly decreases blood pressure. But in general provide a marked degree of cardiovascular stability. Direct depressant effects on the myocardium are minimal.

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PHARMACOKINETIC ASPECTS OF INTRAVENOUS REGIONAL ANAESTHESIA

The exact mechanism of analgesia and muscle paralysis produced by this technique is not clear. It has been suggested that large venous channels that surround the nerve provide access for the drug to the vascular channels in the core of nerves.

SITE OF ACTION

The site and mode of action of the drug is still controversial. The three most probable sites of action are

a. The sensory nerve endings

b. The neuromuscular junction

c. The nerve trunks.

According to **Adams at al (1964)** the anaesthetic solution is for more effective when placed into the isolated vascular tree rather than in the tissues at random. By this method the capillaries perform an important function in the production of anesthesia by transporting the lignocaine very effectively to both large and small nerves. This would explain the rapid decrease in the large nerve conduction speed as well as peripheral anaesthesia which first

appears close to the point of injection. Since lignocaine is effectively shut off from the general circulation it does not reach the liver and is not destroyed. There fore gives anaesthesia as long as it is trapped in the arm. On release of tourniquet the remaining solution seems to be very rapidly flushed out of extremity.

The pharmacokinetic aspects of intravenous regional anaesthesia have been described by **Tucker & Boas (1971).** They described that after cuff release the peak plasma concentration of lignocaine were 20-80% less than when same dose of lignocaine injected by direct intravenous route. The peak level achieved was inversely proportional to total time of the tourniquet applied.

C.J. Evans et al (1974) studied the duration of residual anaesthesia following release of tourniquet after intravenous regional anaesthesia. They found that the duration of block was related to duration of action of the drugs when used clinically. With intravenous regional anaesthesia, the ability of the drug to remain in the nerve in sufficient quantity to cause blockade of the neural transmission is important in regard to residual anesthesia. As the drug reaches the nerve tissue by vascular channels and not by penetrating the nerve sheath, the duration of residual anaesthesia was found to be longest with bupivacaine and shortest with prilocaine. Both the

safety and efficacy of the procedure depend on the interruption of the blood flow to the involved limb.

MATERIALS AND METHODS

This study was conducted in patients undergoing hand surgeries in Thanjavur medical college hospital. The total number of patients was seventy five. After getting institutional ethics committee approval and after explaining the procedure in detail, informed consent obtained from every patient. The patients were assigned in following groups.

Group L: Patients in this group received 40ml of 0.5% lignocaine

Group LS: Patients in this group received 40ml of 0.5% lignocaine and 25µg sufentanil added.

Group LT: Patients in this group received 40ml of 0.5% lignocaine and 100mg tramadol added.

SELECTION OF PATIENTS

The patients selected for this study were of ASA I and II, undergoing elective or emergency hand surgeries.

EXCLUSION CRITERIA

Patient with history of any cardiovascular, respiratory or central nervous system disorders. Patients with haematological disorders like sickle cell anemia, thalasemia. Patients of known hypersensitivity to lignocaine and patients with anticipated difficult airway were excluded from study.

PREANESTHETIC ASSESSMENT

Physical status of all patients was preanaesthetically assessed. A thorough airway assessment done. The following investigations were done on the patients.

INVESTIGATIONS

. Hemoglobin

. Urine analysis

. Blood sugar

. Blood urea & serum creatinine

. Chest x-ray

. Electro cardiogram

RESUSCITATIVE MEASURES

The following resuscitative drugs and equipments were kept ready to meet any emergency.

. Boyle's apparatus

. Laryngoscope with appropriate size blade

. Endotracheal tube of various sizes and connectors

. Suction apparatus

. Drugs like anticonvulsants, antihistamines, vasopressors, steroids and bronchodilators.

PROCEDURE

The patients were shifted into the operation theatre. The pulseoximeter,non-invasive blood pressure monitor and electrocardiographic monitor were connected to patient. All vital parameters were recorded.

A separate intravenous line was started in the non-operative limb. A vein in dorsum of the hand of the operative limb was cannulated with 22G intravenous cannula. If the dorsum of the hand involved in the surgery a vein higher up in the forearm was chosen. It was firmly, fixed, flushed with normal saline and stoppered.

Exsanguination was accomplished by elevation of limbs for 5 minutes followed by use of esmarch bandage from fingertip to arm. In subjects where application of esmarch bandage was not feasible, emptying of veins was facilitated with compression of axillary artery while limb elevated.

At the proximal end of esmarch bandage the first tourniquet was applied around the upper part of the arm over the cotton wool padding. Then the tourniquet was inflated to 250 mmHg. Circulatory isolation of the arm was verified by inspection, absence of radial pulse and loss of pulseoximeter tracing of the ipsilateral index finger. Then 40ml of local anaesthesia solution was injected through the cannula at a rate of 1ml/ second. After the injection of solution the intravenous cannula was removed.

After ensuring complete analgesia below first tourniquet, the second tourniquet was applied distal to the first tourniquet and inflated to 250mmHg. The first tourniquet was removed. The patient was observed for any local anaesthetics toxic manifestations after release of the first tourniquet. The following parameters were recorded.

Time of onset of sensory block:

The time elapsed from injection of study drug to sensory block achieved in all dermatomes. This was checked by pinprick every minute till the onset.

Time of onset of motor block:

The time elapsed from injection of study drug to inability of voluntary movements. This was checked by asking the patient to flex elbow and hand every minute till the onset.

Time of Sensory block recovery:

The time elapsed from tourniquet deflation to recovery of pain in all dermatomes.

Time of motor block recovery:

The time elapsed from tourniquet deflation to ability of voluntary movement

Assessment of tourniquet pain:

Assessment of tourniquet pain was made on the basis of visual analogue scale (VAS), where O = no pain and 10 = worst imaginable pain. Tourniquet pain was measured after tourniquet application and 5,10,20,40 minutes after injection of study drug.

Duration of postoperative pain relief:

The time elapsed from tourniquet release to the first dose of analgesic Inj.diclofenac

Total dose of analgesic:

Total dose of analgesic Inj.diclofenac in mg for the first 24 hours post operatively.

Vital parameters like blood pressure, pulse rate were recorded intra operatively.

At the end of surgery, tourniquet deflation was performed using cyclic deflation method that is the tourniquet was deflated for 3 times for 10 seconds separated by 1 minute interval of reinflation. The patients were carefully observed for possible side effects during and after the release of tourniquet. The tourniquet was not deflated before 30 minutes and was not inflated for more than 90 minutes. The total duration of tourniquet and surgery was noted. The patients were followed up for 24 hours post operatively.

OSERVATION AND RESULTS

Table 1

Age distribution

Age distribution in years	Group L	Group LT	Group LS
< 20	3	3	3
21-30	6	12	16
31-40	9	1	3
41-50	5	7	3
> 51	2	2	0
Total	25	25	25

Mean age in years in group L is 35.2

Mean age in years in group LT is 34.4

Mean age in years in group L Sis 29.3

Table 2

Sex distribution

Sex	Group L	Group LT	*Group LS*

Male Female	19 6	20 5	20 5
Total	25	25	25

Table 3

Weight distribution

Weight in kgs	**Group L**	***Group LT***	**Group LS**
< 50 51-60 > 60	8 14 3	6 12 11	9 11 5
Total	25	25	25

Mean weight in group L is 52.5

Mean weight in group LT is 57.9

Mean weight in group LS is 53.8

Table 4

Time of onset of sensory block

Time of onset of sensory block in minutes	Group L	Group LT	Group LS
< 3 min	0	0	1
3-5 min	13	21	24
6-7min	12	4	0
>7	0	0	0

Meantime and standard deviation of sensory block onset in group L is 5.6±0.93

Meantime and standard deviation of sensory block onset in group LT is 4.8±0.79 and p value is <0.05(statistically significant)

Meantime and standard deviation of sensory block onset in group LS is 3.6±0.61and p value is <0.05(statistically significant)

The mean time required for onset of sensory block on group LS was less than group L and group LT. The mean time required for onset of sensory block on group LT was less than group L.

Table 5

Time of onset of motor block

Time of onset of motor block in minutes	Group L	Group LT	Group LS
< 3	0	0	0
3-5	0	0	13
6-8	8	3	8
8-10	11	21	4
>10	6	1	0

Meantime and standard deviation of motor block onset in group L is 9.28±1.68

Meantime and standard deviation of motor block onset in group LT is 8.88±1.12 and p value is >0.05(statistically not significant).

Meantime and standard deviation of motor block onset in group LS is 6.31±0.3 and the p value is <0.05(statistically significant).

The mean time required for onset of motor block was less in group LS than group L and group LT.

Table 6

Time of sensory block recovery

Meantime and standard deviation of sensory block recovery in group L 5.24±0.64.

Meantime and standard deviation of sensory block recovery in group L 5.16±0.9 and p value is >0.05(statistically not significant)

Meantime and standard deviation of sensory block recovery in group LS 5.08±0.5 and p value is >0.05(statistically not significant)

Meantime required for sensory block recovery in group LS and group LT was not significantly different for group L. These finding showed that addition of sufentanil or tramadol to lignocaine did not affect the sensory block recovery time.

Table 7

Time of motor block recovery

Meantime and standard deviation of motor block recovery in group L

6.48±1.09

Meantime and standard deviation of sensory block recovery in group LT

6.24±1.29 and p value is >0.05(statistically not significant)

Meantime and standard deviation of sensory block recovery in group LS

6.20±1.15 and p value is >0.05(statistically not significant)

Meantime required for motor block recovery in group LS and group LT was not significantly different for group L. These finding showed that addition of sufentanil or tramadol to lignocaine did not affect the motor block recovery time.

Table 8

Mean time of postoperative analgesia

Group	Mean time and SD of post operative analgesia
Group L	191.4±26.96
Group LT	203.8±19.69
Group LS	223.2±14.19

Meantime of post operative analgesia in group LS was more than group L and group LT. p value for group LS is <0.05(statistically significant) and for group LT is >0.05(statistically not significant)

Table 9

Mean dose requirement of analgesic post operatively

Group	Mean dose of post operating
Group L	120±37.49
Group LT	105±38.1
Group LS	90±30.75

Mean dose requirement of analgesic post operatively in group LS was less than group LS group LT. p value for group LS is <0.05(statistically significant) and for group LT is >0.05(statistically not significant)

Table 10

VAS SCORE DURING INTRAOPERATIVE PERIOD (MEDIAN)

There was no difference in VAS score for tourniquet pain before and after tourniquet inflation and at 5, 10, 15 minutes. But at 20 and 40 minutes there was a significant increase in tourniquet pain in group L when compared to other groups.

Table 11

Total duration of surgery

Total duration of surgery in minutes	Group L	Group LT	Group LS
< 40	3	2	3
41-50	8	7	6
51-60	11	15	15
>60	3	1	1

Meantime of surgery in group L : 50.8

Meantime of surgery in group LT: 53.4

Meantime of surgery in group L S: 53.2

Table 12

Total duration tourniquet

Total duration of tourniquet in minutes	Group L	Group LT	Group LS
< 50	3	2	3
51-60	8	7	6
61-70	11	15	15
> 70	3	1	1

Meantime of tourniquet in group L: 60.6

Meantime of tourniquet in group L T: 63.4

Meantime of tourniquet in group L S: 63.4

Table 13

SIDE EFFECTS

Side effects	Group L	Group LT	Group LS
TINNITUS	0	0	0
LIGHT HEADEDNESS	1	0	0
PERIORAL NUMBNESS	1	1	0
VOMITING	1	1	1
NAUSEA	0	0	0
SOMNOLENCE	0	0	4
VERTIGO	0	0	0
SKIN RASHES	0	1	0
ARRHYTHMIAS	0	0	0
CONVULSIONS	0	0	0

In general there were no significant side effects encountered. In group LT there was a case reported skin rash, which was disappeared after two hours post operatively. In group LS there was four cases reported somnolence post operatively.

REVIEW OF LITERATURE

Mona Raafat Fahim et al (2005)

This study was designed to evaluate the effect sufentanil, tramadol or dexmedetomidine added to lignocaine for intravenous regional anaesthesia. They investigated the onset and duration of sensory and motor block, the quality of anesthesia, intra operative and postoperative hemodynamic changes, intra operative and postoperative pain and sedation.

They concluded that addition of sufentanil, tramadol or dexmedetomidine shortened the onset of the sensory block, delayed the onset of tourniquet pain and reduced the intra operative consumption of opioid and dexmedetomidine being the best of the three drugs.

Goel Daftray Pantavaidya et al. (2002)

In their double blind randomized prospective study of 60 adult patients under going upper limb surgeries, they used 30 mg ketorolac or 50mg tramadol with 40ml of 0.5% lignocaine. Intraoperatively the patient's pain score was evaluated using visual analogue scale. All patients were compared for the time to first analgesic dose post operatively. Tramadol was found to be significantly better compared to ketorolac with respect to time to first analgesic and total analgesic used in twenty four hours.

Hoffman el at (1997)

They studied the addition of 25µg sufentanil with 1% prilocaine for upper limb surgeries in 15 patients. They concluded that the addition of 25µg of sufentanil shortened the onset of sensory block compared to control by three minutes. No post operative benefits were demonstrated. Light headedness after tourniquet deflation was reported in 8/15 but this was not analyzed statistically.

Acalovschi et al (2001)

This study looked at the intra operative effects of adding tramadol 100mg with 40ml 0.5% lignocaine. The resultant sensory block (pinprick, touch and temperature) was faster in onset compared to plain lignocaine. However, only touch sensation was slower to recover. Onset and recovery of motor blocked was not affected. Skin rash below the tourniquet that disappeared within one hour of deflation was the only significant side effect. When tramadol was added to lignocaine possible benefit in terms of tourniquet pain and postoperative course were not investigated.

Lai, chang, Yeh et al (1993)

They studied the site of action of lignocaine in intravenous regional anaesthesia. The study was conducted in 15 patients receiving surgical operation on the hands and forearms. Two tourniquets were secured, one on

the arm and another on forearm. Two different concentrations (0.5% and 2%) of lignocaine injected in the intercuff area through 22G cannula and analgesia was observed. The results showed that 0.5% lignocaine produced analgesia in intercuff area only, and in patients received 2% lignocaine experienced analgesia rapidly on the intercuff area and also slowly on the forearm and hand. The anaesthesia developed from fingertips upward. Based on this evidence they concluded that the principal site of action of lignocaine in intravenous regional anesthesia depends on concentration. The lower concentration acts on sensory nerve endings, where as the higher concentration acts on both nerves and nerve endings.

Sulchani, Garcia, Munhall et al. (1989)

In this study the studied cyclic deflation and reinflation of tourniquet at the termination of intravenous regional anaesthesia and safety of the technique by minimizing the peak blood level of local anaesthetic and the time to reach this peak level. They studied in three groups. In the first group the tourniquet was simply deflated and not reinflated. In the second group the tourniquet was deflated for three times with variable time of deflation (0, 10 and 30 seconds) separated by 1minute period of reinflation, and in the third group the tourniquet was deflated for 3 times in fixed period of deflation (10 seconds) separated by 1 minute period of reinflation. The

results obtained indicate that cycling techniques did not appear to significantly reduce peak plasma concentration but cycling techniques significantly prolong the time to reach peak plasma concentration. Of the two cycling methods, the 10 second deflation interval technique appeared to be superior both clinically and pharmacologically.

Stene et al (1995)

In this study they studied presence of peripheral opioid receptors. They concluded that small, systemically inactive doses of exogenous opioids administered in the vicinity of peripheral-nerve terminals have beneficial analgesic effects. Opioid receptors are present on those nerve terminals, and endogenous opioid peptides are detectable in inflamed tissue in both animals and humans. Opioid receptors located on peripheral sensory nerves can be activated by these opioids and mediate the endogenous inhibition of pain. Thus, peripheral opioid receptors can modulate sensory-nerve impulses in a way similar to the action of presynaptic opioid receptors in the spinal cord.

The peripheral action of opioids provides a new approach to pain management. Peripherally acting opioids would allow analgesia without central side effects, such as dysphoria, respiratory depression, sedation,

nausea, or addiction, and without the side effects either of nonsteroidal anti-inflammatory drugs (e.g., renal toxicity and gastric bleeding) or of local anaesthetic drugs (motor- and autonomic-nerve blockade). Whether tolerance to the analgesic effects of peripherally active opioids develops is not known. The fact that peripheral opioid actions are particularly prominent in inflamed tissue may be clinically advantageous, considering that many painful conditions, sub acute or chronic, are associated with inflammation (for example, trauma, postoperative pain, pain due to cancer, and arthritis). In addition to their immunologic functions, immune cells are involved in intrinsic mechanisms of pain inhibition. This involvement may provide new insights into the pain associated with a compromised immune system, as in patients with the acquired immunodeficiency syndrome, cancer, or autoimmune disorders.

DISCUSSION

A better approach for avoidance of general anaesthesia is regional anaesthesia by the use of local anaesthetics. One of such regional anaesthetic technique used in upper limb surgeries is intravenous regional anaesthesia.

This technique was chosen for this study with consideration of following merits and demerits.

Merits:

1. Simple technique – Insertion of IV cannula is the only necessary skill required.
2. Reliable and effective when properly used.
3. Rapid onset of action.
4. Rapid and prompt recovery after tourniquet release.
5. Good analgesia and adequate muscle relaxation
6. Provides blood less operative field.
7. Widely applicable to patients of different ages and physical status for operation of targeting duration.

Demerits:

1. Duration of analgesia is limited by the duration of cuff inflation.

2. Restricted only to extremity surgeries especially distal to elbow and distal to knee in lower limb.
3. Tourniquet is essential prerequisite of the technique.
4. Analgesia cannot be extended to the postoperative period.
5. Tourniquet pain is common.
6. Local anaesthetic toxic reactions like convulsions, coma, cardio respiratory depression and cardiac arrest has been reported following accidental deflation of tourniquet.

Contraindications:

1. Patient refusal
2. Absence of resuscitative equipments and drugs.
3. Allergy to local anesthetics
4. Infection and cellulites in the limb to be blocked
5. Conditions precluding use of tourniquet like
    a. Scleroderma
    b. Hemolytic diseases such as sickle cell anemia, thalasemia
    c. Raynaud's disease
    d. Malignancy
6. Lengthy cases
7. Patients with seizure disorders or with cardiac disorders.

Intravenous regional anaesthesia is an ideal technique for short operative procedures on the extremities. Intravenous regional anaesthesia has been limited by chance of local anaesthetic toxicity, slow onset, poor muscle relaxation, tourniquet pain and minimal post operative pain relief. To improve the quality of intravenous regional anaesthesia, the addition of various opioids to local anaesthetics has been tried.

Pitkanen et al (1992) studied the effect of fentanyl 100 μg with 0.5% prilocaine in intravenous regional anaesthesia for upper limb surgeries. They concluded that the sensory block onset was faster with fentanyl and recovery time was equal, they reported side effects like light-headedness, dizziness and nausea.

Arthur et al (1992) studied sensory block onset and recovery, motor block onset with addition of 100 μg fentanyl with 0.25% lignocaine in intravenous regional anaesthesia. They concluded that the sensory block onset was faster. Sensory recovery and motor block recovery were not affected by addition of fentanyl. There were no side effects reported.

Hoffman et al (1997) studied the addition of sufentanil 25 μg with prilocaine in intravenous regional anaesthesia. They reported that the addition of sufentanil shortened the onset of sensory block compared to control by about three minutes. No postoperative benefits were

demonstrated.

Acalovschi et al (2001) looked at the intra operative effects of adding tramadol 100 mg with 0.5% lignocaine. The resultant sensory block was faster in onset compared to plain lignocaine. Onset and recovery of motor block was not affected.

In our study it was planned to compare efficacy of sufentanil, tramadol added with 0.5% lignocaine in intravenous regional anaesthesia for hand surgeries, and observed the sensory block onset time, sensory block recovery time motor block onset time, motor block recovery time, tourniquet pain, post operative analgesia time and dose requirement of analgesic (diclofenac) post operatively.

In our study there was no significant difference between groups for blood pressure, pulse rate during preoperative and intraoperative time.

In our study the sensory block onset time was more rapid in group LS when compared with group L and group LT. This finding was coincided with the results found by **Hoffman et.al**. The sensory block onset time in group LT was rapid when compared to group L and the same finding was made by **Alayurt et al**. But the sensory block onset time was more in group LT than group LS. These findings showed that addition of sufentanil with lignocaine shortened the onset of sensory block.

The motor block onset time was more rapid in group LS when compared to group L and group LT. This finding was coincided with the results found by **Alayurt et al**. The motor block onset time was shorter in group LT when compared to group L. But when compared to group LS. motor block onset time was longer in group LT.These findings showed that addition of sufentanil with lignocaine shortened the onset of motor block.

In our study, the sensory block recovery time was not different in group LS and group L. This finding coincided with the results derived by **Alayurt et al**. In group LT the sensory block recovery time was not different from group L and this finding correlated with the results found by **Acalovschi et al**. These finding showed that both sufentanil and tramadol did not affect the sensory block recovery time.

The motor block recovery time in group LS was not different from group L. This finding coincided with the findings found by **Hoffman et al**. In group LT the motor block recovery time was not different from group L. This finding coincided with results found by **Acalovschi et al**. These results showed that both sufentanil and tramadol did not affect the motor block recovery time.

In our study, there was no difference between groups in scores for tourniquet pain after tourniquet inflation, and at 5, 10, 15 minutes. But at 20

and 40 minutes there was significant increase in tourniquet pain in-group L when compared with other groups. This finding was correlated with the findings made by **Mona Raafat Fahim et al**. These findings showed that the ability of sufentanil and tramadol in reducing tourniquet pain.

In our study, the duration of postoperative analgesia was longer in group LS than group L and group LT. This finding correlated with results of **Mona Raafat Fahim et al**. In group LT, the duration of post operative analgesia was longer than group L but shorter than group LS. These findings indicated that the addition of sufentanil with lignocaine prolonged the duration of postoperative analgesia.

In our study, the amount of postoperative analgesic (diclofenac in mg) was less in group LS than group L and group LT. These finding coincided with the results of **Mona Raafat Fahim et al**. The amount of post operative analgesic in group LT was less when compared with group L but more when compared with group LS. These findings showed that the addition of sufentanil with lignocaine reduces the amount of postoperative analgesic post operatively.

In our study, it was found that the addition of sufentanil and tramadol to lignocaine in intravenous regional anaesthesia shortened the onset time of sensory block, motor block, delayed the onset of tourniquet pain, lengthened

post operative pain relief and reduced amount of post operative analgesic with out altering sensory block and motor block recovery time. In this regard, sufentanil was more effective in reducing onset time of sensory block, motor block, lengthened postoperative pain relief and reduced amount of postoperative analgesic than tramadol.

CONCLUSION

We conclude that addition of sufentanil and tramadol to lignocaine in intravenous regional anaesthesia shortened the onset time of sensory block, motor block, delayed the onset of tourniquet pain, lengthened post operative pain relief and reduced amount of post operative analgesic drug with out altering sensory block and motor block recovery time. In this regard, sufentanil was more effective than tramadol.

Abdulla WY, Fadhil NM. A new approach to intravenous regional anesthesia. Anesth Analg 1992; 75: 597 –601

1. Armstrong P, Power I, Wildsmith JAW. Addition of fentanyl to prilocaine for intravenous regional anaesthesia. Anaesthesia 1991; 46: 278 –80.
2. Arthur JM, Heavner JE, Mian T, Rosenberg PH. Fentanyl and lignocaine versus lignocaine for Bier block. Reg Anesth 1992; 17: 223 –7.
3. Acalovschi I, Cristea T, Margarit S, and Gavrus R. Tramadol added to lignocaine for intravenous regional anesthesia. Anesth Analg 2001; 92: 209 –14.
4. Alayurt S, Memis D, Pamukcu Z: The addition of sufentanil, tramadol or clonidine to lignocaine for intravenous regional anaesthesia. Anaesth Intensive Care 2004; 32:22–27.
5. Andrew choyce, Philip Peng et al: A systematic review of adjuncts for intravenous regional anesthesia for surgical procedures. Can J Anesth 2002; 49:32-45
6. Brown EM, McGrift.Jt,Malvnowski RW: Intravenous regional anesthesia review of 20 years experience.Can J.Anesth; 1989;36:307-310

7. Clinical anesthesia Paul G.Barash, Bruce F.Cullen, Robert K.Stoelting– 5th Edition.
8. Evans CJ, Dewar JA, Boyce RN, et al: Residual nerve block following intravenous regional anesthesia. BJ Anesthe 1974; 46:668
9. Goel sunita, Daftray, Pantavaidya: Intravenous regional anesthesia using tramadol hydrochloride and ketorolac: A double blind controlled study. Indian J Anesthesia 2002; 46 (5): 369 – 372
10. Gupta B, Brooks JHJ: Narcotic receptors in human peripheral nerves. Aneasthesiology 1989;71:235-40
11. Gissen AJ, Gugino LD, Datta S, et al: Effects of fentanyl and sufentanil on peripheral mammalian nerves. Anesth Analg 1987; 66:1272–1276.
12. Hoffman V, Vercauteren M, Van Steenberge A, Adriaensen H. Intravenous regional anesthesia. Evaluation of 4 different additives to prilocaine. Acta Anaesthesiol Belg 1997; 48: 71 –6.
13. Mona Raafat Fahim: The addition of sufentanil, Tramadol or dexmedetomidine to lignocaine for intravenous regional anesthesia. Eng J Anesthe 2005; 21: 283 - 288
14. McGlone R, Heyes F, Harris P. The use of a muscle relaxant to supplement local anesthetics for Bier's blocks. Arch Emerg Med

1988; 5: 79 –85.

15. . Miller's Anesthesia – Ronald D Miller. 6th Edition.
16. Pitkänen MT, Rosenberg PH, Pere PJ, Tuominen MK, Seppälä TA. Fentanyl-prilocaine mixture for intravenous regional anaesthesia in patients undergoing surgery. Anaesthesia 1992; 47: 395 –8.
17. Pharmacology and physiology in Anaesthetic Practice, Robert K.Stoelting. 3rdedition
18. Reuben SS, Steinberg RB, Kreitzer JM, Duprat KM. Intravenous regional anesthesia using lignocaine and ketorolac. Anesth Analg 1995; 81: 110 –3.
19. .Raj PP, Garcia CE, Burleson JW,ET al: The site of action of intravenous regional anesthesia.Anesth Analg 1972;51;776
20. Regional Anesthesia in infants, Children and adolescent. Bernard Dalens I edition
21. Starzk F, Thiocoipé M, Favarel-Garrigues JF, Lassié P, Petitjean ME, Dabadie P. The use of 0.25% lignocaine with fentanyl and pancuronium for intravenous regional anesthesia. Anesth Analg 1997; 84: 777–9
22. Stein C. The control of pain in peripheral tissue by opioids. N Engl J Med 1995; 332: 1685 –90

23. Sukhani R, Garcia C, Munhall R. Lignocaine disposition following intravenous regional anesthesia with different tourniquet deflation techniques. Anesth Analg 1989; 68: 633-7.

24. Tan SM, Pay LL, Chan ST: Intravenous regional anaesthesia using lignocaine and tramadol. Ann Acad Med Singapore 2001; 30:516–519.

25. Text book of Anesthesia. Alan Aitkenhead, David J Rowbotham, Graham Smith 4th edition

26. Text book of Regional anesthesia – P.Prithiviraj M.D., Churchill Livingstone

27. Wylie – A practice of Anesthesia Wylie and Churchill Davidson's 7th Edition.

PROFORMA

INTRAVENOUS REGIONAL ANAESTHESIA USING LIGNOCAINE ,SUFENTANIL AND TRAMADOL

NAME: AGE: IPNO:

SEX: WEIGHT:

DIAGNOSIS: PROCEDURE:

HISTORY:

STARVATION:

PRE OPERATIVE EXAMINATION:

PULSE RATE: CVS:

BLOOD PRESSURE: RS:

TEMPERATURE: CNS:

ABDOMEN:

INVESTIGATIONS:

Hb: BLOOD SUGAR: UREA: CREATININE:

ECG: X RAY CHEST: OTHERS:

AIRWAY:

ASA PHYSICAL STATUS:

PATIENT GROUP: LIGNOCAINE / LIGNOCAINE WITH SUFENTANIL/ LIGNOCAINE WITH TRAMADOL

TOURNIQUET:

INFLATION TIME: DEFLATION TIME:

SENSORY BLOCK ONSET TIME: (MIN)

MOTOR BLOCK ONSET: (MIN)

INTRA OP HEMODYNAMICS

	1 MIN	5MIN	10MIN	20MIN	40MIN	60MIN	75MIN	90MIN
PR								
BP								

INTRA OP TOURNIQUET PAIN: AT 5 MIN 10MIN 20 MIN 40 MIN (VAS)

SUPPLEMENTATION OF GA DUE TO T.PAIN: YES / NO

TOTAL DURATION OF TOURNIQUET: (MIN)

TOTAL DURATION OF SURGERY: (MIN)

SENSORY BLOCK RECOVERY TIME: (MIN)

MOTOR BLOCK RECOVERYTIME: (MIN)

TOTAL DURATION OF POST OP ANALGESIA: (MIN)

POST OP ANALGESIA WITH RESCUE DRUG GIVEN: YES / NO

TOTAL DOSE OF ANALGESIC GIVEN: (mgs)

ADVERSE EFFECTS:

TINNITUS	:	YES / NO
LIGHT HEADEDNESS	:	YES / NO
PERIORAL NUMBNESS	:	YES / NO
VOMITING	:	YES / NO
NAUSEA	:	YES / NO
SOMNOLENCE	:	YES / NO
VERTIGO	:	YES / NO
SKIN RASHES	:	YES / NO
ARRHYTHMIAS	:	YES / NO
CONVULSIONS	:	YES / NO